AF/3738
EDW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor :	Wenda C. Carlyle	
Appln. No.:	09/014,087	Group Art Unit: 3738
Filed :	January 27, 1998	
For :	PROSTHESES WITH ASSOCIATED GROWTH FACTORS	Examiner: Paul B. Prebilic
Docket No.:	S16.12-0062	

AMENDED BRIEF FOR APPELLANT

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5 DAY OF June, 2006

Hallie R. Finnegan
PATENT ATTORNEY

Dear Sir:

This Amended Brief is presented in response to the Examiner's Answer mailed on April 5, 2006 and in support of the Notice of Appeal filed November 16, 2005, from the final rejection of claims 1, 2, 4-11, 14, 15, and 21-28 of the above-identified application, as set forth in the Office Action mailed June 16, 2005.

I. REAL PARTY OF INTEREST

The Real Party of Interest is St. Jude Medical, Inc., a corporation organized under the laws of the state of Minnesota, and having offices at One Lillehei Plaza, St. Paul, MN 55117, has acquired the entire right, title and interest in and to the invention, the application, and any and all patents to be obtained therefor, as set forth in the Assignment filed with the patent application and recorded on Reel 8997, Frame 0357.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences for the above-referenced patent application.

III. STATUS OF CLAIMS

I.	Total number of claims in the application.		
		Claims in the application are:	1-29
II.	Status of all the claims.		
	A.	Claims cancelled:	3, 12, 13, 16-20 and 29
	B.	Claims withdrawn but not cancelled:	None
	C.	Claims pending:	1, 2, 4-11, 14, 15 and 21-28
	D.	Claims allowed:	None
	E.	Claims rejected:	1, 2, 4-11, 14, 15 and 21-28
	F.	Claims Objected to:	None
III.	Claims on appeal		
		The claims on appeal are:	1, 2, 4-11, 14, 15 and 21-28

IV. STATUS OF AMENDMENTS

No amendment was filed subsequent to the final rejection.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The subject matter of claim 1 is described in embodiments throughout the specification, for example, on at least page 4, line 10 to page 16, line 30. Specifically, the prosthesis includes allograft or xenograft tissue (at least page 8, lines 19-23 and page 20, line 22 – page 25, line 26 (Example 1)) having a polypeptide growth factor associated with the tissue (at least page 3, lines 16-18; page 6, lines 4-6) by means of a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations (at least page 6, lines 23-26; page 12, lines 15-17; page 13, lines 15-20, page 14, lines 12-16 and page 15, lines 5-8), said

polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue (at least page 3, lines 15-17 and 28-30; page 6, line 27 – page 7, line 3 and page 20, lines 9-11).

Claim 14 defines a prosthetic heart valve comprising a substrate with associated VEGF, where the prosthesis has a valve structure (at least page 5, lines 1-2; page 7, lines 5-7, 10-13, 16-21; page 9, line 30-page 12, line 12 and page 20, line 22 – page 25, line 26 (Example 1)). The VEFG is associated with the substrate by direct attachment, a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations (at least page 6, lines 20-26; page 12, lines 15-17; page 13, lines 15-20; page 14, lines 13-16 and page 20, line 22 – page 25, line 26 (Example 1)) where the polypeptide growth factors are effective to stimulate the affiliation of viable cells with said substrate (at least page 3, lines 15-17 and 28-30, page 6, line 27 – page 7, line 3; and page 20, lines 9-11).

Claim 25 is directed to a prosthesis comprising crosslinked natural tissue (at least page 6, lines 10-12; page 7, lines 14-30 and page 8, lines 12-23) having an exogenous polypeptide growth factor associated therewith (at least page 6, lines 4-7; page 12, line 15 – page 14, line 22 and page 20, line 22 – page 25, line 26 (Example 1)).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 25 and 28 are properly rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,308,641 ("Cahalan patent").

B. Whether claims 25 and 26 are properly rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, as being unpatentable under 35 U.S.C. §103(a) as being obvious over European Patent Application No. EP 0476983 ("Bayne application").

C. Whether claims 1-2, 4-5, and 9-11 are properly rejected under 35 U.S.C. § 103(a) as being obvious over the Bayne application in view of U.S. Patent No. 5,631,011 ("Wadström patent").

D. Whether claims 6-8, 14, 15, 21-24 and 27-28 are properly rejected under 35 U.S.C. § 103(a) as being obvious over the Bayne application and the

Wadström patent in view of U.S. Patent No. 4,648,881 ("Carpentier patent").

VII. ARGUMENT

A. The Examiner Erroneously Rejected Claims 25 and 28 Under 35 U.S.C. §102(b) as Being Anticipated by the Cahalan Patent.

The Examiner erroneously rejected claims 25 and 28 under 35 U.S.C. §102(b) as being anticipated by the Cahalan patent. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, all claim elements, and their limitations, must be found in the prior art reference to maintain a rejection based on 35 U.S.C. §102.

Independent claim 25 defines the present invention as a prosthesis comprising crosslinked natural tissue having an exogenous polypeptide growth factor associated therewith. The Cahalan patent does not disclose associating an exogenous polypeptide growth factor with crosslinked natural tissue. Therefore, the Cahalan patent does not disclose each and every element of claim 25 and does not anticipate claim 25.

In the Final Office Action mailed on June 16, 2005, the Examiner erroneously alleged that the Cahalan patent discloses human or animal tissue being used as the solid surface and that the biomolecule is one of the growth factors listed, citing the following excerpts from the Cahalan patent (col. 6, lines 14-18; the abstract; col. 4, lines 20-43; and col. 6, lines 8-28). The Examiner further alleged that the terms "fixed" and "crosslinked" are synonymous in the tissue graft art and that glutaraldehyde is disclosed as a crosslinking agent in the Cahalan patent at column 4, lines 58-62. The Examiner also alleged that when glutaraldehyde contacts the tissue solid surface, it **inherently** crosslinks the tissue and results in a crosslinked or fixed tissue as claimed. (Emphasis added).

In contrast to the Examiner's interpretation of the Cahalan patent, Applicants assert that the Cahalan patent discloses a lightly crosslinked spacer (polyalkylimine that is attached to a solid surface) for the purpose of improving biocompatibility. (Col. 4, lines 14-19 and 68). The polyalkylimine is first applied to the solid surface and then is treated with the crosslinking agent. (Col. 6, lines 29-31). The polyalkylimine is reacted with a crosslinking agent such that the reaction is completed in a few minutes. (Col. 5, lines 9-10) The crosslinking agent is used to lightly crosslink the polyalkylimine for the purpose of providing a polyalkylimine surface that allows a cellular adhesive molecule or other biomolecule to bond to the spacer. (Col. 4, line 62 – Col. 5, line 3; Col. 6, lines 8-10).

There is no disclosure in the Cahalan patent of a crosslinked natural tissue for association with an exogenous polypeptide growth factor. While the Cahalan patent does disclose a crosslinking agent, as the Examiner alleges in the Office Action, the Examiner fails to take into account the portion of the Cahalan patent following the passage upon which the Examiner relied that discloses the crosslinking is to be limited to the spacer molecules. The Cahalan patent discloses as follows:

> The spacer of the present invention can therefore be made by applying a polyalkylimine to the solid surface and then **treating the applied polyalkylimine with the cross-linking agent**. Preferably, the cross linking agent used to **crosslink the polyalkylimine** is applied in a dilute solution and at a suitable pH to **accomplish light crosslinking** and to provide aldehyde functionality for the polyalkylimine surface that will allow biomolecules to readily bond to the spacer.

(Col. 4, line 62-Col. 5, line 3)(Emphasis added). There is no disclosure in the Cahalan patent of a crosslinked natural tissue as alleged by the Examiner. Rather, the Cahalan patent discloses a lightly crosslinked polyalkylimine spacer. The purpose of cross-linking the spacer is to provide a stable platform for attachment of the biomolecule while preventing the biomolecule from becoming buried in the spacer layer and losing bioactivity. (Col. 2, lines 63-66 and Col. 3, lines 63-65). Therefore, the Cahalan patent teaches the attachment of the biomolecule to the spacer and teaches away from attaching the biomolecule to the tissue as claimed in claim 25.

Further, contrary to the Examiner's allegation, polyalkylimine, the only material that is disclosed as being crosslinked in the Cahalan patent, is not a natural tissue

simply because it is connected to a natural tissue. Polyalkylimine is not a natural tissue because it bonds to natural tissue. To make this assertion would lead the Examiner to conclude that a titanium plate inserted into a bone would be natural tissue once the bone and the titanium plate bonded. Just as one would not consider titanium to be a natural tissue, polyalkylimine cannot be considered a natural tissue just because it attaches to natural tissue.

A natural tissue is derived from an animal species, typically mammalian, such as human, bovine, porcine, seal, or kangaroo (pg. 7, lines 14-16). As stated above, the polyalkylimine is a spacer that attaches to a natural tissue to provide a stable platform for attachment of the biomolecule. An element of claim 25 is to associate a exogenous polypeptide growth factor with a crosslinked natural tissue. The Cahalan patent does not disclose each and every element of claim 25, and therefore does not anticipate claim 25.

The Examiner also alleges that the glutaraldehyde solution as disclosed in the Cahalan patent **inherently** crosslinks the natural tissue. To allege inherency, the Examiner must meet the burden of proof that what is asserted must necessarily happen. *See* M.P.E.P. § 2112.

"The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier,* 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" *In re Robertson,* 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed Cir. 1999). "In relying upon the theory of inherency, the Examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent

characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). (Emphasis added)

The Examiner alleges in the Office Action that when it (glutaraldehyde) contacts the tissue solid surface, it (glutaraldehyde) inherently crosslinks the tissue, resulting in a crosslinked or fixed tissue as claimed. However, the Examiner has not provided any technical reasoning to reasonably support the assertion that a dilute concentration glutaraldehyde solution will crosslink with tissue in the few minutes, as set forth in the Cahalan patent. (Col. 5, lines 3-10). *See Ex parte Levy*, 17 USPQ2d at 1464.

The Examiner also referred to Example 1 in the Carpentier patent in Response to Arguments. Example 1 in the Carpentier patent disclosed that porcine aortic heart valve tissue was fixed with 0.625 weight percent solution of glutaraldehyde. However, there is no indication in the Carpentier patent of the amount of time that was necessary to fix the porcine aortic heart valve with the glutaraldehyde solution.

Applicants do not dispute that with enough time and at adequate concentrations, glutaraldehyde will fix a tissue as disclosed in the Carpentier patent. However, Applicants disagree with the Examiner's unsupported allegation that a dilute concentration glutaraldehyde solution will crosslink tissue in the few minutes as disclosed in the Cahalan patent.

Applicants have previously provided the Examiner with an excerpt from Collagen, Volume III, Biotechnology, CRC Press, pp. 2, 3 and 13 which indicates that fixing tissue with glutaraldehyde takes hours to occur. An additional copy of the excerpt is attached hereto as Exhibit A in Appendix B. Thus, Applicants have provided third party technical data that indicates that crosslinking or fixing a natural tissue with glutaraldehyde requires several hours to complete, not just a few minutes as disclosed in the Cahalan patent. The Examiner's posits or any other allegations, without a basis in fact and/or technical reasoning, do not support an allegation of inherency. *See Ex parte Levy,* 17 USPQ2d at 1464. Therefore, the Examiner has not satisfied the burden of proof to allege that a dilute glutaraldehyde solution fixes a natural tissue in a few minutes as disclosed in the Cahalan patent. As such, the Examiner erred in finally rejecting claim 25 as being anticipated by the Cahalan patent since the tissue will not be fixed.

Claim 28 depends from independent claim 25, and was also rejected under 35 U.S.C. §102(b) as being anticipated by the Cahalan patent. While Appellants do not acquiesce with the particular rejections to claim 28, it is believed that this rejection is moot in view of the remarks made in connection with independent claim 25. Claim 28 includes all of the limitations of claim 25, and recites additional features which further distinguish it from the cited reference. Therefore, the Examiner erred in rejecting claim 28 as being anticipated by the Cahalan patent.

B. The Examiner Erroneously Rejected Claims 25 and 26 as being Anticipated, or Alternatively, Made Obvious by the Bayne Application and Erroneously Rejected Claims 27 and 28 as being Made Obvious by the Combination of the Bayne Application in view of the Wadström Patent.

The Examiner erroneously rejected independent claim 25 as being anticipated by or, alternatively, as being unpatentable under 35 U.S.C. §103(a) over the Bayne application by itself. The standard for a proper 35 U.S.C. §102(b) rejection was provided in Section A. The standard for a proper 35 U.S.C. §103(a) rejection is as follows:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. §103(a).

> Under Section 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966),

When applying 35 U.S.C. §103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(D) Reasonable expectation of success is the standard with which obviousness is determined.
Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Claim 25 defines the present invention as a prosthesis comprising crosslinked natural tissue having an exogenous polypeptide growth factor associated therewith. The Bayne application does not disclose associating an exogenous polypeptide growth factor with crosslinked natural tissue. The Bayne application does not disclose each and every element of claim 25 and therefore does not anticipate or make claim 25 obvious.

In the Final Office Action mailed on June 16, 2005, the Examiner erroneously alleged that the Bayne application discloses a fibrin coating being applied prior to or in addition to a VEGF II growth factor to a surface of a fixed umbilical cord vein. The Examiner also erroneously speculates (posits) that the tubular supports coated with VEGF II include fixed umbilical cord vein, and thus anticipates claim 25 where the attachment of the cells to the vessel is done prior to implantation such that the claim language requiring growth factor associated with the tissue is fully met.

Applicants respectfully disagree with the Examiner's characterization of the disclosure of the Bayne application. The Bayne application does not disclose a fibrin coating being applied prior to or in addition to a VEGF II growth factor to a surface of a fixed umbilical cord vein. Rather, the Bayne Application discloses growing cells in a culture in the presence of VEGF II, removing the cells from the culture and then plating the cells on fixed umbilical cord vein (page 8, lines 15-19). This is clearly different from claim 25 where the VEGF is associated with the natural tissue. Therefore, the Examiner erred in rejecting claim 25 as being anticipated by the Bayne application.

The Examiner also alleged that the Bayne application makes claim 25 unpatentable as being obvious. The Examiner posits (assumes) that it would have been clearly obvious to use umbilical cord vein as the tubular support since it is used as an

implant in another procedure; it would bring the desired features of tissue properties to the implant site. Furthermore, a combination of proteins such as fibrin, and growth factor (VEGF II) would have been at least obvious in view of the Bayne application alone since the teachings of doing the same are all contained in the same paragraph and there is no clear delineation between them.

The Examiner erred in rejecting claim 25 as being obvious over the Bayne Application because the Examiner has failed to meet his initial burden of establishing a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P §2142. The Examiner's assumption used to allege that claim 25 is obvious does not meet the standard for modifying a reference as set forth in case law.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). (Emphasis added)

Applicants submit that the Examiner used the language of claim 25 as a roadmap to combine aspects of two separate preparation procedures disclosed in the Bayne application for implanting two dissimilar materials, a natural vessel and an artificial vessel. Of note, claim 25 is directed to a prosthetic comprising crosslinked **natural** tissue. Therefore, the procedure for preparing an **artificial** vessel is not relevant to claim 25.

The Examiner combined associating fibrin and growth factor, which was disclosed as being coated on an **artificial** vessel, with the preparation of a **natural** tissue (fixed umbilical cord vein). However, the Bayne application only discloses coating the **natural** tissue (fixed umbilical cord vein) with endothelial cells (not growth factor)

prior to implanting. There is no teaching or suggestion to combine a method of preparing an **artificial** vessel with a method of preparing a **natural** tissue, absent the present invention, which is impermissible.

The Examiner erred in his reasoning for combining the two separate and dissimilar procedures for preparing dissimilar materials when it was stated that "the teaching of doing the same are all contained in the same paragraph and there is no clear delineation between them." A statement that modifies the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). The mere fact that elements of a claim are located in the same reference in proximity to each other does not meet the Examiner's burden for modifying the reference.

Further, Applicants disagree with the Examiner's characterization of the Bayne application that the two separate and distinct procedures or embodiments are not delineated. The Bayne application at page 8, line 20 starts the sentence with the word "Alternatively." By definition, the word "alternative" means a choice between two mutually exclusive possibilities. *See* The American Heritage Dictionary of the English Language, p.55, Houghton Mifflin Company, (3rd Ed. 1992) attached hereto as Exhibit B in Appendix B. Since the two procedures are mutually exclusive or alternatives in Bayne, it is improper for the two procedures to be combined.

Finally, the Examiner posits (assumes) that since umbilical cord vein is used as an implant in another procedure, it would bring the desired features of tissue properties to the implant site. The Bayne Application discloses how to prepare both a natural vessel (coating with endothelial cells only) and an artificial vessel (coating with proteins, such as fibrin, and a growth factor (VEGF II)) by distinctly different and mutually exclusive procedures.

There is no teaching in the Bayne application to combine the two distinctly separate procedures for preparing dissimilar materials for implantation as alleged by the

Examiner. Therefore, the Examiner erred in rejecting claim 25 as being obvious over the Bayne application.

Claim 26 depends from independent claim 25, and was also rejected under 35 U.S.C. §102(b) and 35 U.S.C. §103(a) as being unpatentable over the Bayne application. While Appellants do not acquiesce with the particular rejections to claim 26, it is believed that this rejection is moot in view of the remarks made in connection with independent claim 25. Claim 26 includes all of the limitations of claim 25, and recites additional features which further distinguish it from the cited reference. Therefore, the Examiner erred in rejecting claim 26 as being anticipated or made obvious by the Bayne application.

Claims 27 and 28 were rejected as being obvious over the Bayne application and the Wadström patent and further in view of the Carpentier patent. Claims 27 and 28 depend from claim 25. While Appellants do not acquiesce with the particular rejection to claims 27 and 28, it is believed that this rejection is moot in view of the remarks made in connection with independent claim 25. The combination is improper since the two separate preparation procedures are still being combined by the Examiner. Claims 27 and 28 include all of the limitations of claim 25, and recites additional features which further distinguish it from the cited references. Therefore, the Examiner erred in rejecting claim 27 and 28 as being obvious over the Bayne application and the Wadström patent and further in view of the Carpentier patent.

C. The Examiner Erroneously Rejected Claims 1-2, 4-5, and 9-11 under 35 U.S.C. § 103(a) as being Unpatentable over the Bayne Application in view the Wadström Patent and Erroneously Rejected Claims 6-8 under 35 U.S.C. § 103(a) as being Unpatentable over the Combination of the Bayne Application and the Wadström Patent in view of the Carpentier Patent.

The Examiner erroneously rejected independent claim 1 as being obvious over the Bayne application in view of the Wadström patent. Claim 1 defines the present invention as a prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, the polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue. The Bayne application in view of the Wadström

patent does not disclose a prosthesis for a human patient comprising **allograft or xenograft** tissue having polypeptide growth factor associated therewith. Therefore, the Bayne application in view of the Wadström patent does not make claim 1 obvious.

In the Final Office Action mailed on June 16, 2005, the Examiner erroneously alleged that the Bayne application discloses an implant having a fibrin coating (a biologic adhesive as claimed) which is applied prior to the VEGF II growth factor. The Examiner also alleged that fixed umbilical cord vein as disclosed in the Bayne application is the substrate for coating as claimed. The Examiner alleged that the fixed umbilical cord as disclosed in the Bayne application, while not clearly either an allograft or a xenograft, is generic to both. The Examiner finally alleges that it would have been considered clearly obvious to an ordinary artisan to use an allograft or xenograft tissue for the cord vein as disclosed in the Bayne application absent some showing of criticality therefore. The Examiner alleges that the Wadström patent discloses that fibrin is a common biologic tissue adhesive in the art and therefore, the fibrin coating as disclosed in the Bayne application would function as a biologic adhesive as claimed.

Applicants respectfully disagree with the Examiner that claim 1 is obvious over the Bayne application in view of the Wadström patent. Elements of claim 1 include a prosthesis for a human patient comprising **allograft or xenograft** tissue having polypeptide growth factor associated therewith. An allograft tissue is defined in the specification as tissue of a different individual of the same species. (Page 8, lines 21-23). A xenograft tissue is defined in the specification as tissue from a species different from the patient's species. (Page 8, lines 19-21). Therefore, allograft tissue and xenograft tissue are natural tissues.

The Examiner again improperly combined the two mutually exclusive preparation procedures, one for natural tissue and one for an artificial vessel, disclosed in the Bayne application to improperly allege that the Bayne application discloses coating fixed umbilical cord vein with fibrin and growth factor. Applicants incorporate the arguments made above with respect to claim 25 in Section B of this Appeal Brief to prove that the Examiner improperly modified the Bayne application and that the Examiner has not met his burden of proving prima facie obviousness.

To reiterate, the Bayne application does not disclose coating fibrin and growth factor on fixed umbilical cord vein. Rather, the Bayne application discloses coating fibrin and growth factor on an artificial vessel. An artificial vessel is neither an allograft tissue nor a xenograft tissue as defined in claim 1. Therefore, the Bayne application does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, such as fibrin.

The Wadström patent does not disclose allograft tissue or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, such as fibrin. The Examiner has not explained how the use of fibrin can be incorporated into the procedure for a natural tissue as disclosed in the Bayne application. The Bayne application only discloses coating an artificial vessel with fibrin. However, an artificial vessel is not an allograft or xenograft tissue as defined in claim 1. Therefore, the combination of the Bayne application with the Wadström patent is not proper and the Examiner erred in rejecting claim 1 as being obvious.

The Examiner rejected claims 2, 4-5, and 9-11 as being obvious over the Bayne application in view of the Wadström patent and claims 6-8 as being obvious over the Bayne application and the Wadström patent in view of the Carpentier patent. As above, Carpentier relates to natural tissue, and thus the combination of the two procedures is improper. Claims 2 and 4-11 are dependent from claim 1. While Appellants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claim 1. These dependent claims include all of the limitations of claim 1 and any intervening claims, and recite additional features that further distinguish these claims from the cited references. Therefore, the Examiner erred in rejecting claims 2 and 4-11 as being obvious.

D. The Examiner Erroneously Rejected Claims 14, 15 and 21-24 under 35 U.S.C. § 103(a) as being unpatentable over the Combination of the Bayne Application and the Wadström Patent in view of the Carpentier Patent.

The Examiner erroneously rejected claims 14, 15 and 21-24 under 35 U.S.C. § 103(a) as being unpatentable over the combination of the Bayne application and the Wadström patent in view of the Carpentier patent. Claim 14 defines the present

invention as a prosthetic heart valve comprising a substrate with associated VEGF, wherein said VEGF is associated with the substrate by direct attachment, a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the prosthesis having a valve structure, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said substrate.

In the Final Office Action mailed on June 16, 2005, the Examiner erroneously alleged that while the Bayne application fails to disclose uncrosslinked tissue, the heart valve form of tissue, or other types of tissue claimed, the Carpentier patent teaches that all uncrosslinked and crosslinked forms of tissue, heart valve tissue forms and other types of tissue are known in the art. The Examiner then alleges that it would have been obvious to use any of the materials disclosed in the Carpentier patent as the substrate of the Bayne application for the applications contemplated by the Carpentier patent. The Examiner also alleged that one would be motivated to form the implants disclosed in the Bayne application into other shapes to make it useful in other sites and broaden its applicability.

Applicants respectfully disagree with the Examiner that claim 14 is obvious over the Bayne application in view of the Wadström patent and the Carpentier patent. Again, the Examiner improperly modified the Bayne application to combine mutually exclusive methods of preparing a **natural** tissue for implantation with the method for preparing an **artificial** vessel for implantation as previously discussed above with respect to independent claims 1 and 25.

The Carpentier patent discloses many different **natural** tissues that can be used as heart valve prostheses. (Emphasis added). There is no reason to combine the tissues disclosed in the Carpentier patent with the mutually exclusive method of preparation disclosed the Bayne Application for an artificial substrate. "In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

The tissue disclosed in the Carpentier patent is natural tissue. As such, the tissue disclosed in the Carpentier patent as applied to the disclosure of the Bayne application would be prepared by plating cells that were grown in vitro in a VEGF II solution, and then the tissue would subsequently be implanted into the patient. Prior coating with fibrin would not be done.

The combination of the Bayne application with the Carpentier patent would not provide a prosthetic heart valve comprising a substrate associated with VEGF as claimed in claim 14. Therefore, the Bayne application in view of the Wadström patent and the Carpentier patent does not make claim 14 obvious.

Further, the Examiner improperly used claim 14 as a roadmap to allege obviousness. Claim 14 relates to a prosthetic heart valve. The Examiner cites the Bayne application as the primary reference. However, the Bayne application does not disclose the implanting of a heart valve, but rather the preparation of artificial and natural blood vessels for implantation.

In fact, when this issue was addressed in a previous communication, the Examiner responded in the June 16, 2005 Final Office Action that the motivation to combine the references was "[o]ne would be motivated to form Bayne et al implants into other shapes in order to make it useful in other sites and broaden its applicability." "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Broadening the applicability of a reference beyond its disclosure is not a permissible reason to combine references. The Examiner's stated purpose for combining the Bayne application with the Carpentier patent is an improper combination.

Finally, the Examiner states that the Bayne application is drawn to all types of vascular tissue repair. The Examiner then alleges that tissue heart valves are a type of vascular graft. (See Office Action mailed on December 13, 2004, p.9). However, a definition of a vascular graft is "tube replacement of an artery or vein segment". Joseph D. Branzino, The Biomedical Engineering Handbook, Second Edition, Vol. II, p. 128-8, CRC Press (2000). (Exhibit C in Appendix B). Thus, a heart valve prosthesis does not fall within the definition of a vascular graft. Therefore, the Examiner has improperly

stated that heart valve implants (cardiac implants) are vascular grafts and cannot equate a disclosure for a blood vessel implant with a heart valve prosthetic.

As such, the combination of the Bayne application and the Wadström patent with the Carpentier patent is an improper combination. Therefore the Examiner erred in rejecting claim 14 as being obvious over the Bayne application in view of the Wadström patent and the Carpentier patent.

The Examiner rejected claims 15 and 21-24 as being obvious over the Bayne application in view of the Wadström patent and the Carpentier patent. Claims 15 and 21-24 depend from independent claim 14. While Applicants do not acquiesce with the particular rejections to these dependent claims, it is believed that these rejections are moot in view of the remarks made in connection with independent claims 14 and 25 above. These dependent claims include all of the limitations of the base claim and any intervening claims, and recite additional features which further distinguish these claims from the cited references. Therefore, the Examiner erred in rejecting claims 15 and 21-24 as being obvious.

Applicants will consider filing a terminal disclaimer in the event that co-ending application Serial No. 09/186,810 issues into a patent. Therefore, the provisional double patenting rejection is moot.

Conclusion

Appellants respectfully submit that claims 1-2, 4-11, 14-15, and 21-28 are patentable over the cited prior art. It is respectfully requested that the rejections be reversed, and that all pending claims 1-2, 4-11, 14-15 and 21-28 be allowed.

Respectfully submitted,

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Appendix A

CLAIMS INVOLVED IN APPEAL:

1. (previously presented) A prosthesis for a human patient comprising allograft or xenograft tissue having a polypeptide growth factor associated therewith by a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme substrate associations, said polypeptide growth factor being effective to stimulate the affiliation of viable cells with said tissue.

2. (original) The prosthesis of claim 1 wherein said binding of said polypeptide growth factor to said tissue involves specific binding interactions.

3. Canceled

4. (original) The prosthesis of claim 1 wherein said binding of said polypeptide growth factor to said tissue involves a linker molecule.

5. (original) The prosthesis of claim 1 wherein said tissue comprises crosslinked tissue.

6. (original) The prosthesis of claim 1 wherein said tissue comprises uncrosslinked tissue.

7. (original) The prosthesis of claim 1 wherein said tissue comprises a porcine heart valve.

8. (original) The prosthesis of claim 1 wherein said tissue comprises bovine pericardial tissue.

9. (original) The prosthesis of claim 1 wherein said polypeptide growth factor comprises vascular endothelial growth factor.

10. (original) The prosthesis of claim 9 wherein said vascular endothelial growth factor comprises a protein selected from the group consisting of bVEGF164, bVEGF120, hVEGF165, hVEGF121, VEGF II, VEGF-B, VEGF2, modified active forms thereof, and combinations thereof.

11. (original) The prosthesis of claim 1 wherein said tissue comprises synthetic tissue.

12-13 Canceled

14. (previously presented) A prosthetic heart valve comprising a substrate with associated VEGF, wherein said VEGF is associated with the substrate by direct attachment, a biologic adhesive, antibody-antigen associations, specific binding protein-receptor associations or enzyme-substrate associations, the prosthesis having a valve structure, said polypeptide growth factors being effective to stimulate the affiliation of viable cells with said substrate.

15. (previously presented) The prosthetic heart valve of claim 14 wherein said prosthetic heart valve comprises a porcine heart valve.

16-20. Canceled

21 (previously presented) The prosthetic heart valve of claim 14 wherein the substrate comprises tissue.

22. (previously presented) The prosthetic heart valve of claim 21 wherein said tissue comprises uncrosslinked tissue.

23. (previously presented) The prosthetic heart valve of claim 21 wherein said tissue comprises crosslinked tissue.

24. (previously presented) The prosthetic heart valve of claim 14 wherein the substrate comprises a synthetic polymer.

25. (previously presented) A prosthesis comprising crosslinked natural tissue having an exogenous polypeptide growth factor associated therewith.

26. (previously presented) The prosthesis of claim 25 wherein said polypeptide growth factor comprises vascular endothelial growth factor.

27. (previously presented) The prosthesis of claim 25 wherein said crosslinked tissue comprises a crosslinked heart valve.

28. (previously presented) The prosthesis of claim 25 wherein said crosslinking involves glutaraldehyde moieties.

29. Canceled

Appendix B

Evidence Index

Applicant has submitted no evidence under 37 C.F.R. §§ 1.130, 1.131 or 1.132 through the prosecution of this application.

Applicant submitted an excerpt from Collagen, Volume III, Biotechnology, pp. 2, 3 and 13, CRC Press, Inc. (1988), in an Amendment mailed on August 23, 2004 and a Response After Final mailed on October 17, 2005, which is attached hereto as Exhibit A (5 pages).

Applicant submitted the definition for the word "alternative" as printed in The American Heritage Dictionary of the English Language, p. 55, Houghton Mifflin Company, (3rd Ed. 1992) in Response After Final mailed on October 17, 2005, which is attached hereto as Exhibit B (3 pages).

Applicant submitted a definition of "vascular graft" printed in The Biomedical Engineering Handbook, Second Edition, Vol. II, p. 128-8, CRC Press (2000) in an Amendment mailed March 14, 2005, which is attached hereto as Exhibit C (3 pages).

COLLAGEN

Volume III
Biotechnology

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I. INTRODUCTION

Collagen fibers constitute the fundamental structural framework of our tissues and organs. Collagen is also the single most abundant protein, and accounts for around 30% of all proteins present in mammals.[1] Collagen is deposited rapidly during periods of rapid growth, and its rate of synthesis declines with age particularly in tissues that undergo little remodeling. The intracellular synthetic process, which leads to the synthesis of procollagen, is relatively complex since it involves a series of posttranslational modifications.[1] The catabolic pathway is modulated by the activity of the enzyme collagenase. In between these two extreme events, there is a process of maturation and cross-linking which provides the collagen fibrils with mechanical and biological stability. The collagen molecules can be extracted from tissues and reconstituted into fibrils or the tissues themselves (heart valves, tendons, pericardium, etc.) can be cross-linked and stabilized for use as bioprosthesis. It is this concept that prompted us to attempt to use such tissues as well as various forms of reconstituted collagen, collagen composites, or modified collagen products as bioprosthetic replacements.

Our own interest in this area began in 1966 following our observation that glutaraldehyde could introduce stable cross-links into collagen fibers devoid of native cross-links.[2] Other aldehydes tested, such as formaldehyde, were not as effective, nor did they generate the thermally and chemically stable cross-links introduced by glutaraldehyde.

The practical application of this concept in our laboratory was prompted in 1969 by Warran Hancock who suggested that the porcine heart valve could, if properly handled, provide suitable prosthetic replacements for diseased tissues. Aware of earlier failures of formaldehyde to accomplish this task, we decided to use glutaraldehyde.[3,4] A very simple experiment was devised to rapidly test a variety of agents for their ability to stabilize the collagen framework of vascular tissues. Porcine aortic valves, with surrounding muscular and connective tissues, were fixed in a variety of reagents which included formaldehyde, crotonaldehyde, acetaldehyde, and glutaraldehyde, and other aldehyde analogues under various conditions of ionic strength, pH, and temperature. Tissues were transferred to a large container and exposed to running water at room temperature. Most tissues began to disintegrate rapidly. After a few weeks, the only tissues that failed to show macroscopic and microscopic structural degeneration were those treated with glutaraldehyde at neutral pH.

These rather simple and direct observations stimulated us to develop more refined tests to quantitate the physical, chemical, and biological stability of the cross-links introduced by glutaraldehyde into collagen. Various testing procedures were designed, which confirmed the above studies.[5-7] Biomechanical studies, heat of denaturation and associated shrinkage, enzymatic degradation, etc. proved the cross-linked material to be satisfactory and encouraged the implantation of the first such valves fixed with glutaraldehyde later that year into humans.[8-10] Similar studies were being conducted independently by Carpentier and associate in Paris, which resulted in the implantation into humans of the first glutaraldehyde cross-linked prosthesis.[11]

The success that followed when cross-linked xenografts generated functional heart valve

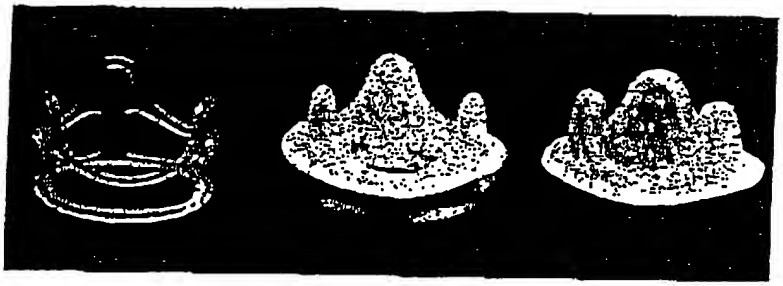

FIGURE 1. Basic components used to assemble one of the early versions of a Hancock valve: a machine tooled polypropylene stent, a sewing ring, and a glutaraldehyde cross-linked porcine aortic valve.

replacement stimulated considerable interest in this technology. This approach is now applied successfully to other prosthetic materials such as skin, tendons and ligaments, pericardial patches, collagen implants, etc. Many interesting findings and several problems have arisen over the years of follow-up of patients with such collagen derived implants. These include fibrotic infiltration, matrix degeneration, calcification, immune rejection, sensitization, toxicity of unreacted glutaraldehyde, thrombosis, and infection. These events have stimulated our laboratory as well as many others to look at various aspects of the chemistry and biology of the implanted material and the host response.

Our earlier studies were followed by attempts to understand the chemistry and reactivity of glutaraldehyde with model compounds and monomeric and polymeric collagen.[12-14] Concomitantly, we continued to investigate the biological compatibility of glutaraldehyde cross-linked collagen with cells, tissues, and body fluids while we attempted to chemically modify the surface of the fibrils and covalently attach macromolecules to the insoluble matrix.[15] In particular, we have been interested in serum proteins (albumin) in glycosaminoglycans (chondroitin sulfate) and diphosphonates (3-amino-1-hydroxypropane-1,1-diphosphonic acid or APD) as a means of preventing or inhibiting the calcification of collagen implants, a major reason for failure of the devices. A variety of in vitro nucleation and calcium uptake tests were adapted to this purpose, as well as implant studies in animals. The compatibility of glutaraldehyde cross-linked collagen with cells and tissues has been investigated using tissue culture techniques and subcutaneous implantation into rats of different ages. The blood-surface interphase was studied using scanning electron microscopy, platelet aggregation, and ATP release assays. The biological stability of cross-linked tissues and reconstituted collagen fibrils and that of chemically modified preparations was investigated in rats histologically and by in vitro enzyme digestion assays. This enabled us to assess the degree of cross-linking and resistance to biological degradation of the collagen implant. The immunogenicity of cross-linked collagen derived from bovine tissues was investigated in rabbits using procedures developed specifically for these studies to overcome the high degree of insolubility of the cross-linked antigen. The studies summarized in this communication represent the combined efforts of many investigators who shared the common interest of further understanding the chemistry and biology of collagen in relationship to its biomaterial properties. Some of the bioprostheses that have originated from the application of the technology are illustrated in Figures 1, 2, and 3.

II. CHEMISTRY OF GLUTARALDEHYDE

A. Reaction of Model Amino Compounds with Glutaraldehyde

Equal molar ratios of 6-aminohexanoic acid and glutaraldehyde (0.05 *M*) were allowed

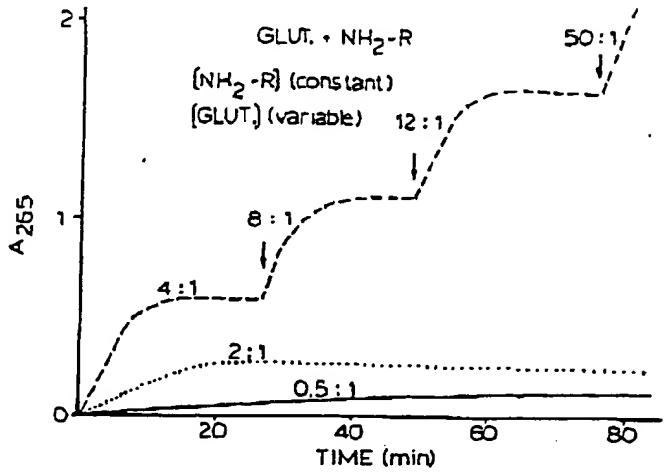

FIGURE 8. Time course of the formation of the 265 nm absorbing products in reaction mixtures containing a constant amount of 6-aminohexanoic acid (0.01 *M*) and increasing amounts of glutaraldehyde: (—) 0.04 *M* glutaraldehyde (4:1), (...) 0.02 *M* glutaraldehyde (2:1), (—) 0.005 *M* glutaraldehyde (0.5:1). Arrows indicate new additions of fourfold or more excess of glutaraldehyde at each indicated time point. Numerical ratios reflect the relative molar concentrations of glutaraldehyde:6-aminohexanoic acid at each point in the total reaction mixture.

in the number of lysyl residues modified. This reflects an increase in the molecular length of the glutaraldehyde polymers extending from the initial glutaraldehyde and lysyl residue reaction sites rather than an increase in the actual number of cross-linking sites. These conclusions arise from the observation that after free glutaraldehyde becomes depleted from the solution by binding to reactive groups, subsequent addition of glutaraldehyde molecules causes these to add to those already reacted (Figure 8). When this occurs on the surface of collagen molecules, this reaction will give use to large molecular weight polymers of glutaraldehyde that will now be able to generate "long range cross-links" between further removed reactive sites.

B. Cross-Linking of Collagen in Tissue Matrices

When dealing with fixation of tissues or of densely packed molecules such as collagen fibers, additional variables were introduced. Under these circumstances, penetration of the glutaraldehyde molecules and accessibility to the reactive group on the proteins became a significant issue.[31] When dealing with whole tissues, this becomes a matter of concern even more so. Penetration at room temperature is definitely faster than in the cold. Glutaraldehyde (2%) penetrates into soft animal tissues (i.e., liver) 0.7 mm in 3° hr at room temperature, while its ability to produce adequate fixation lags behind since it reaches a depth of only 0.5 mm in the same period of time. After 24° hr, glutaraldehyde penetrates to a depth of 1.5 mm, while good fixation reaches to a depth of 1.0 mm. However, the maximum penetration of human liver by 4% glutaraldehyde in 24° hr at room temperature and in the cold was 4.5 mm and 2.5. mm, respectively.[32] Other investigators have also presented data on the penetration rate of glutaraldehyde into rat liver.[32-35] A mixture of glutaraldehyde (2%) and formaldehyde (2%) was shown to penetrate human liver to depths of 2.0, 2.5, and 5.0 mm in 4, 12, and 24° hr, respectively.[35]

This relatively slow rate of tissue penetration and the uncertainty of its degree of reactivity as the distance from the surface increases, can cause problems when fixing tissues for electron

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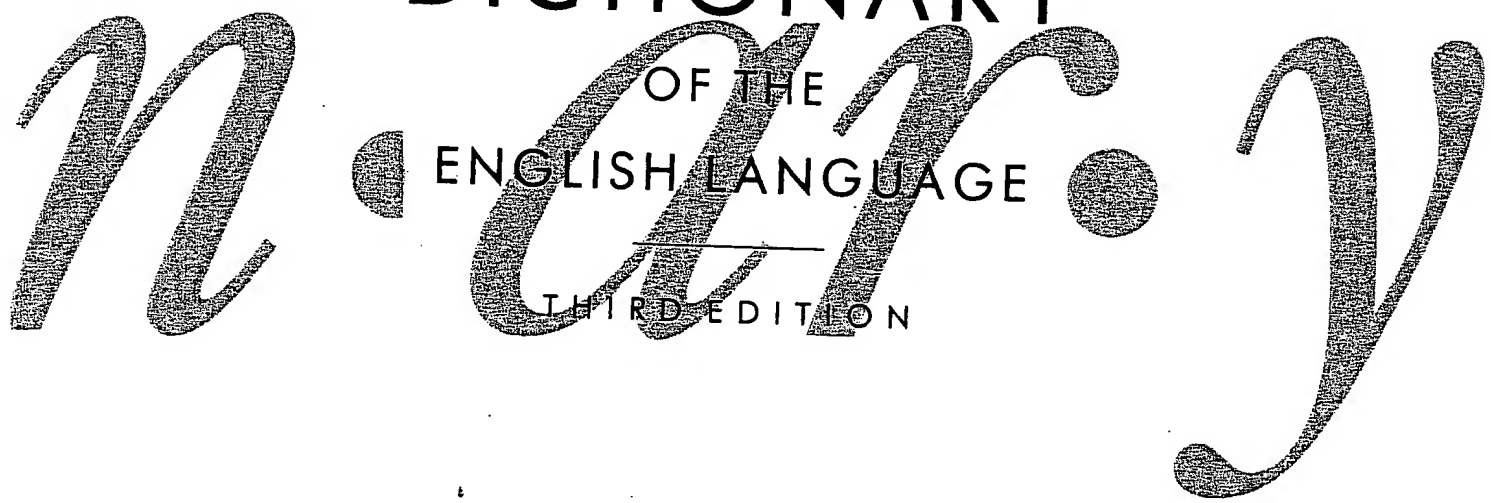

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when worshipers may come forward to make or renew a profession of faith. Also called ♦ *invitation*.

al·tar·piece (ôl′tər-pēs′) *n.* A piece of artwork, such as a painting or carving, that is placed above and behind an altar.

altar rail *n.* A railing in front of the altar that separates the chancel from the rest of a church.

Al·tay Mountains (ăl′tī′). See **Altai Mountains.**

alt·az·i·muth (ăl-tăz′ə-məth) *n.* **1.** A mounting for astronomical telescopes that permits both horizontal and vertical rotation. **2.** A telescope having such a mounting. [ALT(ITUDE) + AZIMUTH.]

Alt·dorf (ălt′dôrf). A town of central Switzerland near the southeast tip of the Lake of Lucerne. A statue commemorates the legendary exploits of William Tell, marking the spot where he supposedly shot an apple off his son's head. Population, 8,200.

Al·ten·burg (ăl′tən-bûrg′, -bōork′). A city of east-central Germany south of Leipzig. It was built on the site of early ninth-century Slavic fortifications. Population, 54,999.

al·ter (ôl′tər) *v.* **-tered, -ter·ing, -ters.** —*tr.* **1.** To change or make different; modify: *altered my will.* **2.** To adjust (a garment) for a better fit. **3.** To castrate or spay (an animal, such as a cat or a dog). —*intr.* To change or become different. [Middle English *alteren*, from Old French *alterer*, from Medieval Latin *alterāre*, from Latin *alter*, other. See **al-**[1] in Appendix.]

al·ter·a·ble (ôl′tər-ə-bəl) *adj.* That can be altered: *alterable clothing; alterable conditions of employment.* —**al′ter·a·bil′i·ty, al′ter·a·ble·ness** *n.* —**al′ter·a·bly** *adv.*

al·ter·a·tion (ôl′tə-rā′shən) *n. Abbr.* **alt. 1.** The act or procedure of altering. **2.** The condition resulting from altering; modification.

al·ter·a·tive (ôl′tə-rā′tĭv, -tər-ə-tĭv) *adj.* **1.** Tending to alter or produce alteration. **2.** *Medicine.* Tending to restore to normal health. —**alterative** *n. Medicine.* A treatment or medication that restores health.

al·ter·cate (ôl′tər-kāt′) *intr.v.* **-cat·ed, -cat·ing, -cates.** To argue or dispute vehemently; wrangle. [Latin *altercārī, altercāt-*, to quarrel, from *alter*, other. See **al-**[1] in Appendix.]

al·ter·ca·tion (ôl′tər-kā′shən) *n.* A vehement quarrel.

alter ego *n.* **1.** Another side of oneself; a second self. **2.** An intimate friend or a constant companion. [Latin : *alter*, other + *ego*, I, self.]

al·ter·nar·i·a (ôl′tər-nâr′ē-ə, ăl′-) *n.* Any of various fungi in the genus *Alternaria*, many of which cause plant diseases, chiefly blights and leaf spots. [New Latin, genus name, from Latin *alternus*, alternate. See ALTERNATE.]

al·ter·nate (ôl′tər-nāt′, ăl′-) *v.* **-nat·ed, -nat·ing, -nates.** —*intr.* **1.** To occur in successive turns: *showers alternating with sunshine.* **2.** To pass back and forth from one state, action, or place to another: *alternated between happiness and depression.* —*tr.* **1.** To do or execute by turns. **2.** To cause to follow in turns; interchange regularly. —**alternate** (-nĭt) *adj.* **1.** Happening or following in turns; succeeding each other continuously: *alternate seasons of the year.* See Usage Note at **alternative. 2.** Designating or relating to every other one of a series: *alternate lines.* **3.** Serving or used in place of another; substitute: *an alternate plan.* **4.** *Botany.* **a.** Arranged singly at each node, as leaves or buds on a stem. **b.** Arranged regularly between other parts, as stamens between petals. —**alternate** (-nĭt) *n. Abbr.* **alt. 1.** A person acting in the place of another; a substitute. **2.** An alternative. [Latin *alternāre, alternāt-*, from *alternus*, by turns, from *alter*, other. See **al-**[1] in Appendix.] —**al′ter·nate·ly** *adv.* —**al′ter·nate·ness** *n.*

al·ter·nate angle (ôl′tər-nĭt, ăl′-) *n. Mathematics.* One of a pair of nonadjacent angles on opposite sides of a transversal that cuts two lines. The angles are both exterior or both interior to the two lines.

alternate host *n.* **1.** One of two species of host on which some pathogens, such as certain rust fungi, must develop to complete their life cycles. **2.** A species of host other than the principal host on which a parasite can survive.

al·ter·nat·ing current (ôl′tər-nā′tĭng, ăl′-) *n. Abbr.* **ac, AC** An electric current that reverses direction in a circuit at regular intervals.

al·ter·na·tion (ôl′tər-nā′shən, ăl′-) *n.* Successive change from one thing or state to another and back again.

alternation of generations *n.* The regular alternation of forms or of mode of reproduction in the life cycle of an organism, such as the alternation between diploid and haploid phases, or between sexual and asexual reproductive cycles. Also called *metagenesis, xenogenesis.*

al·ter·na·tive (ôl-tûr′nə-tĭv, ăl-) *n.* **1.a.** The choice between two mutually exclusive possibilities. **b.** A situation presenting such a choice. **c.** Either of these possibilities. See Synonyms at **choice. 2.** *Usage Problem.* One of a number of things from which one must be chosen. —**alternative** *adj.* **1.** Allowing or necessitating a choice between two or more things. **2.a.** Existing outside traditional or established institutions or systems: *an alternative lifestyle.* **b.** Espousing or reflecting values that are different from those of the establishment: *an alternative newspaper; alternative greeting cards.* —**al·ter′na·tive·ly** *adv.*

USAGE NOTE: Some traditionalists hold that *alternative* should be used only in situations where the number of choices involved is exactly two, because of the word's historical relation to Latin *alter*, "the other of two." H.W. Fowler, among others, has considered this restriction a fetish. The Usage Panel is evenly divided on the issue, with 49 percent accepting the sentence *Of the three alternatives, the first is the least distasteful.* • *Alternative* is also sometimes used to refer to a variant or substitute in cases where there is no element of choice involved, as in *We will do our best to secure alternative employment for employees displaced by the closing of the factory.* This sentence is unacceptable to 60 percent of the Usage Panel. • *Alternative* should not be confused with *alternate.* Correct usage requires *The class will meet on alternate* (not *alternative*) *Tuesdays.*

alternative school *n.* A school that is nontraditional, especially in educational ideals, methods of teaching, or curriculum.

al·ter·na·tor (ôl′tər-nā′tər, ăl′-) *n.* An electric generator that produces alternating current.

al·the·a also **al·thae·a** (ăl-thē′ə) *n.* **1.** See **rose of Sharon** (sense 1). **2.** See **hollyhock.** [Latin, mallows, from Greek *althaia*, from *althainein*, to heal. See **al-**[2] in Appendix.]

alt·horn (ălt′hôrn′) or **Alt·horn** *n. Music.* Any of several upright, valved brass wind instruments used especially in bands. [German : *alt*, alto (from Italian *alto*; see ALTO) + *Horn*, horn, from Middle High German, from Old High German. See **ker-**[1] in Appendix.]

al·though also **al·tho** (ôl-*th*ō′) *conj.* Regardless of the fact that; even though. [Middle English : *al*, all; see ALL + *though*, though; see THOUGH.]

USAGE NOTE: As conjunctions, *although* and *though* are generally interchangeable: *Although* (or *though*) *she smiled, she was angry. Although* is usually placed at the beginning of its clause (as in the preceding example), whereas *though* may occur elsewhere and is the more common term when used to link words or phrases, as in *wiser though poorer*, or in constructions such as *Fond though* (not *although*) *I am of opera, I'd rather not sit through the* Ring *cycle this weekend.*

al·tim·e·ter (ăl-tĭm′ĭ-tər) *n.* An instrument for determining elevation, especially an aneroid barometer used in aircraft that senses pressure changes accompanying changes in altitude. [Latin *altus*, high; see **al-**[2] in Appendix + —METER.] —**al′ti·met′ric** (ăl′tə-mĕt′rĭk) *adj.* —**al·tim′e·try** *n.*

al·ti·pla·no (ăl′tĭ-plä′nō) *n., pl.* **-nos.** A high plateau, as in the Andean regions of Bolivia, Peru, and Argentina. [American Spanish : Latin *altus*, high; see **al-**[2] in Appendix + Latin *planum*, plain; see PLANE[1].]

al·ti·tude (ăl′tĭ-tōod′, -tyōod′) *n. Abbr.* **alt. 1.** The height of a thing above a reference level, especially above sea level or above the earth's surface. See Synonyms at **elevation. 2.** A high location or area. **3.** *Astronomy.* The angular distance of a celestial object above the horizon. **4.** The perpendicular distance from the base of a geometric figure to the opposite vertex, parallel side, or parallel surface. **5.** High position or rank. [Middle English, from Latin *altitūdō*, from *altus*, high. See **al-**[2] in Appendix.] —**al′ti·tu′di·nal** (-tōod′n-əl, -tyōod′-) *adj.*

altitude sickness *n.* A collection of symptoms, including shortness of breath, headache, and nosebleed, brought on by decreased oxygen in the atmosphere, such as that encountered at high altitudes.

al·to (ăl′tō) *n., pl.* **al·tos.** *Abbr.* **A.** *Music.* **1.** A low, female singing voice; a contralto. **2.** A countertenor. **3.** The range between soprano and tenor. **4.** A singer whose voice lies within this range. **5.** An instrument that sounds within this range. **6.** A vocal or instrumental part written for a voice or an instrument within this range. —*attributive.* Often used to modify another noun: *an alto flute; an alto balalaika.* [Italian, from Latin *altus*, high. See **al-**[2] in Appendix.]

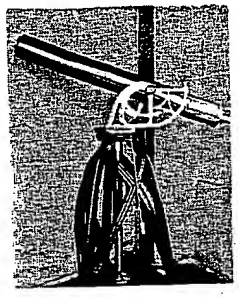
alto clef *n. Music.* The C clef positioned to indicate that the third line from the bottom of a staff represents the pitch of middle C.

al·to·cu·mu·lus (ăl′tō-kyōō′myə-ləs) *n.* A cloud formation of rounded, fleecy, white or gray masses. [Latin *altus*, high; see **al-**[2] in Appendix + CUMULUS.]

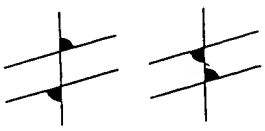
al·to·geth·er (ôl′tə-gĕth′ər) *adv.* **1.** Entirely; completely; utterly: *lost the TV picture altogether; an altogether new approach.* **2.** With all included or counted; all told: *There were altogether 20 people at the dinner.* **3.** On the whole; with everything considered: *Altogether, I'm sorry it happened.* —**altogether** *n.* A state of nudity. Often used with *the*: *in the altogether.* [Middle English *al togeder* : *al*, all; see ALL + *togeder*, together; see TOGETHER.]

USAGE NOTE: *Altogether* should be distinguished from *all together. All together* is used of a group to indicate that its members performed or underwent an action collectively: *The nations stood all together. The prisoners were herded all together. All together* can be used only if it is possible to rephrase the sentence so that *all* and *together* may be separated by other words: *The books lay all together in a heap. All the books lay together in a heap. Altogether* should be used only when the sense could be expressed by *entirely* or *completely.*

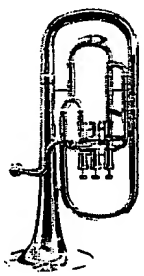
Al·ton (ôl′tən). A city of southwest Illinois on bluffs of the Mississippi River north of St. Louis, Missouri. Lewis and Clark spent the winter of 1803–1804 just south of the site. Population, 34,171.



altazimuth
Mid 18th-century Russian telescope built by Mikhail V. Lomonosov (1711–1765)



alternate angle



althorn

ă pat	oi boy
ā pay	ou out
âr care	o͝o took
ä father	o͞o boot
ĕ pet	ŭ cut
ē be	ûr urge
ĭ pit	th thin
ī pie	*th* this
îr pier	hw which
ŏ pot	zh vision
ō toe	ə about, item
ô paw	♦ regionalism

Stress marks: ′ (primary); ″ (secondary), as in **dictionary** (dĭk′shə-nĕr′ē)

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Neointimal hyperplasia: Fibroblast and smooth-muscle cell growth covering a vascular graft on the inside surface.

Pannus: Neointimal hyperplasia tissue ingrowth at the anastomoses.

Pseudointimal hyperplasia: Fibrin/thrombin deposition on the inside surface of an arterial vascular graft. This accumulation of material is acellular.

Stenosis: Tissue ingrowth into vessel causing a narrow lumen and reduction of blood flow.

Vascular graft: Tube replacement of an artery or vein segment.

Vascular reconstruction: Reconstruction of an artery or vein after trauma, surgery, or blockage of blood flow from disease.

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Appendix C

Related Proceedings Index

None.